REMARKS

Allowable Subject Matter

In the February 10, 2004 Office Action, the Office found the claimed subject matter of claim 35 to be allowable if rewritten in independent form. In the Advisory Action of August 6, 2004, the Office found that claim 35 was not amended properly. Applicants have amended claim 35 thereby placing it in condition for allowance.

Rejection of Claims and Traversal Thereof

In the Advisory Action of August 6, 2004, the following rejections were maintained:

claims 1-2, 9, 12, 23-25, 27-28 and 33-34 were rejected under 35 U.S.C. §112, first paragraph; and

claim 12 was rejected under 35 U.S.C. §102(a) and (b) as being anticipated by Seki, et al., 1998, Saito, T. et al., 1999, or Naik, M. U., et al., 1999, Genbank Sequence Database (Accession No: Q9Z0F4).

These rejections are hereby traversed and reconsideration of patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. §112, first paragraph

According to the Office, the arguments presented in the response filed on April 10, 2004 would not be considered because the claims would not be entered. Applicants do not completely understand why the claims were not entered except for the fact that there was a limited amount of time for the Office to give applicants arguments sufficient time to review. Applicants are requesting that the Office review the remarks set forth herein and determine that all claims, including method and product claims, that recite conservative substitutions at amino acid residue 127 or 172 in SEQ ID NO: 2, be found allowable.

Applicants have adequately described, at pages 36 and 37 of the present specification, the process involved in the mutations in the two Ca^{2+} -binding EF-hands and that the mutations were created by the QuikChange site-directed mutagenesis method (Stratagene) using the pBS-calmyrin construct with

PCR primers EF(N)1 (SEQ ID NO: 21) and 2 (SEQ ID NO: 22) or EF(C)1 (SEQ ID NO: 23) and 2 (SEQ ID NO: 24) to generate, respectively, the D127N mutation by changing the first base in the codon from G to A and the E172Q mutation by changing the first base in the codon from G to C. Specifically, in the calmyrin-EF-N mutant the aspartic acid at position 127 of protein SEQ ID NO: 2 in the first intact EF-hand in calmyrin was mutated to asparagine (G to A at position 445 of nucleotide SEQ ID NO: 26) . Similarly, the calmyrin-EF-C mutant had the glutamic acid at position 172 of protein SEQ ID NO: 2 in the second intact EF-hand mutated to glutamine (G to C at position 584 of nucleotide SEQ ID NO: 26). The acidic residues were replaced with their amine counterparts. Thus, one skilled in the art could easy practice applicants' claimed invention.

Further, Applicants have shown the effectiveness of the mutations at the 127 and 172 residues, especially in the reduction in apoptosis relative to that caused by presenilin 2. Initially, it should be noted that Applicants were the first to discover the calcium binding protein "calmyrin." The protein was identified as "calmyrin" because the name describes its inherent properties without bias towards its multiple binding partners. Applicants discuss on page 20 of the specification the process used to discover the calmyrin protein (SEQ ID NO: 2) and that it was named by its interaction with the PS2-loop B bait construct. As stated in the specification, applicants named the calcium binding protein "calmyrin" because is was shorter than using the complete terminology "calcium-binding myristoylated protein with homology to calcinerurin." Further, applicants discovered that calmyrin was ubiquitously expressed in all tissues that were examined which implies that it plays a common function in most if not all cells.

Clearly, once applicants discovered this protein, the next step in the process was to determine how to reduce the affinity between presenilin 2 and calmyrin thereby altering the cell death cascade to reduce the effects of cell death, especially in neuronal cells of FAD patients. Applicants set about, as shown with the multiple experiments set forth in the specification, to determine effective mutations in the calmyrin (SEQ ID NO 2) and presenilin 2 (SEQ ID NO: 1) that would reduce the affinity of calmyrin for presenilin 2 or at least modulate the interaction between the two proteins so that the normal triggering of the cell death cascade would be averted or at least reduced.

As such, several mutations were found to be effective in reducing the affinity of calmyrin for presenilin 2 and/or modulating the interaction between the two proteins so that the normal triggering of the cell death cascade would be averted or at least reduced. These mutations for calmyrin include:

1) substituting at least one amino acid residue in the calcium-binding EF-hands of SEQ ID NO: 2, wherein the calcium-binding hands including amino acid residues at positions 116 to 128 and 161 to 173 of SEQ ID NO: 2;

2) substituting at least one N-terminal residue at position 1 to 3 of SEQ ID NO: 2; and

3) substituting at least one amino acid residue at position 2, 127 and/or 172 of SEQ ID NO: 2.

Currently the mutation at 127 in the calcium-binding EF-hands of SEQ ID NO: 2 is being examined and applicants are expecting that Examiner Davis will also examine mutation at 172 in light of the fact that there is no prior art that defeats the patentability of such a mutation. As discussed above, at page 33 there is a discussion as to how the nucleotide sequence of calmyrin (SEQ ID NO: 26) was altered to introduce the mutations at certain amino acid residues, including amino acid residues 127 or 172. The mutated calmyrin was then tested for affinity with presenilin 2 and it was found that there was reduced affinity between the proteins and reduced cell death was evident.

As shown and discussed at page 39 of the present specification, coexpression of wild type calmyrin with PS2 increased cell death additively (seen in both Fig. 39 and Fig. 40), coexpression of the 127 and 172 mutants **with PS2 decreased cell death below the 2.09 level seen with PS2 alone**. When compared to PS2, the decrease in cell death from the coexpression of the EF-hand mutants reached statistically significance, EF-C mean=1 .05 (p-value=0.006) and EF-N mean=1 .00 (p-value=0.005). Thus applicants have shown that these mutations in the EF-hand amino acid residues reduce cell death *in vitro*.

Applicants insist that to be enabling, the specification must simply set forth "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. Applicants have met this standard.

Applicants have provided sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention by discussing the exact regions for mutations in the calmyrin protein that have been found effective to reduce apoptosis. Specifically, as stated above, these regions include: the calcium-binding EF-hands of SEQ ID NO: 2, specifically mutations at residue 127 or 172 of SEQ ID NO: 2. It is well settled in the law that a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to

be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. The Office has not provided any evidence that one of ordinary skill in the art would doubt the objective truth of the statements contained in applicants' disclosure, and thus, all claims as now amended meet the requirements under 35 U.S.C. §112, first paragraph, and withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. §102(a) and (b)

Claim 12 was rejected under 35 U.S.C. §102(a) and (b) as being anticipated by Seki, et al. 1998, Saito, T. et al. 1999, or Naik, M. U., et al. 1999, Genbank Sequence Database (Accession No: Q9Z0F4). It should be noted that all three references disclosed the same sequence, albeit not anticipatory of applicants' claimed invention. Applicants respectfully traverse this rejection and submit that applicants' claimed invention is not anticipated by the cited references.

To anticipate a claim or render it obvious, a reference must be enabling. This point was recently reaffirmed in an April 7, 2000 decision of the Court of Appeals for the Federal Circuit (CAFC).[1] Citing *In re Paulsen*,[2] the court stated that to be anticipating, a prior art reference must:

1) disclose each and every limitation of the claimed invention;

2) be enabling; and

3) describe the claimed invention sufficiently to place it in possession of a person of ordinary skill in the field of the invention.

The cited references do no meet this standard.

Applicants' claim 12 reads as follows:

> 12. (Currently amended) A purified mutant calcium-binding protein comprising an amino acid sequence as set forth in SEQ ID NO: 2 and having a conservative substitution at residue 127 or 172.

According to the Office:

[1] *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000).
[2] *In re Paulsen*, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994).

> "Concerning Applicant's argument that the cited reference lack enablement and as such cannot be anticipatory, it is noted that the amino acid sequence taught by prior art seems to be the same as the claimed mutant, and thus inherently would have the same material, structural and functional characteristics of the claimed mutant. Therefore the issue of enablement is not germane here."

Initially, it should be noted that the amino acid sequence of the cited references is not the same as that of applicants' SEQ ID NO: 2. As shown below there are ten (10) different amino acid residues and thus the sequences are not identical.

m1 is prior art

h1 is applicants' claimed SEQ ID NO: 2

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m1 mggsgsrlsk ellaeyqdlt fltkqeilla hrrfcellpp eqrtveeslh trvsfeqils
h1 mggsgsrlsk ellaeyqdlt fltkqeilla hrrfcellpq eqrtvesslr aqvpfeqils

m61 lpelkanpfk eridmvfsts ptrdslsfed fldllsvfsd tatpdikshy afrifdfddd
h61 lpelkanpfk eridrvfsts pakdslsfed fldllsvfsd tatpdikshy afrifdfddd

m121 gtldredlsq lvncltgege dtrlsasemk qlidnilees didrdgtinl sefqhvisrs
h121 gtlnredlsr lvncltgege dtrlsasemk qlidnilees didrdgtinl sefqhvisrs

m181 pdfassfkiv l
h181 pdfassfkiv l
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Thus, it is the Office's position that even though there are multiple differences between the cited art sequence and SEQ ID NO. 2, the Office contends that the sequences are the same and would have similar structural and functional characteristics. Clearly, the sequences are not the same. Moreover, this position is in sharp contrast to statements made in the September 25, 2002 Office Action wherein the Office required an election of species between mutations in the calcium binding hands because the Office found one mutation to be patentably distinct from another mutation. Thus, the Office found that one change in the amino acid sequence inevitably caused a patentably distinct species and as such applicants were forced to select a single species to be prosecuted. Clearly this reasoning should be extended to a sequence wherein there are ten residue differences between the cited art sequence and SEQ ID NO: 2. However, instead, the Office contends they are not patentably distinct and that the mouse sequence of the cited references anticipates SEQ ID NO: 2. Applicants vigorously disagree and submit that sequence of the cited references does not identically disclose, teach or suggest applicants' claimed sequence SEQ ID NO 2. As such, the cited references cannot be considered as

anticipatory because they do not "identically disclosed or described" the presently claimed invention as required of an anticipatory reference applied under section 102. (See *In re Felton*, 179 USPQ 295 (CCPA 1973)).

Moreover, the Office has not provided any evidence on how a person of ordinary skill in the art would read the sequence of the cited references and understand what changes are needed in the sequence listing to arrive at the mutated sequence of applicants' claimed SEQ ID NO: 2 without an undue amount of experimentation. *See In re Sheppard*, 144 USPQ 42, (CCPA 1981) (reversing a rejection under 35 U.S.C. Section 102(b) where the asserted prior art reference did not permit someone skilled in the art to possess the claimed invention). For example, where in the mouse sequence is there any teaching or suggestion for introducing a substitution at residue 127 or 172? Further, even if by some serendipitous stroke of luck there was a substitution at these residues, the overall mouse sequence of the cited references is not that of SEQ ID NO: 2. Clearly, the references are not enabling and do not put the claimed invention in the hands of one skilled in the art. (*In re Sun*, 31 USPQ2d 1451 (Fed. Cir. 1993)).

Further, applicants should not be held to a standard that they must prove that the mouse sequence of the prior art does not inherently exhibit the same characteristics as that of mutated SEQ ID NO: 2 when the sequences are not even the same, and thus, the Office would be merely speculating that maybe the protein would have the same structural or functional characteristics as that of SEQ ID NO: 2.

Accordingly, applicants respectfully submit that claim 12 patentably distinguishes over the sequence of the cited references. Withdrawal of this rejection under 35 U.S.C. §102(a) and (b) is requested.

Reconsideration of Election of Species

Applicants request that the Office reconsider the required Election of Species imposed in the September 25, 2002 Office Action between mutations at amino acid residue 127 and 172. Applicants have shown that a mutation at either residue is novel and is not anticipated by the cited references. The sequence listing disclosed by the cited references does not identically disclose SEQ ID NO. 2 and/or mutations at residue 127 or 172. Moreover, applicants have shown that the mutation at 172 of SEQ ID NO. 2 has the ability to reduce apoptosis relative to Presenilin-2. Thus, the method claims are enabling.

Further, the two substitutions were originally presented as a Markush group in claim 12 and according to MPEP §803.02:

> "if the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct invention."

Still further, the two substitutions at 127 and 172 residues meet the requirements of unity of invention because they are included in a Markush group and the mutations share a common utility and share a substantial structural feature disclosed as being essential to that utility. No prior art was found that anticipates or renders obvious the elected species 127 mutation, and as such, the search of the Markush group should be extended to that of the 172 mutation. As already stated above, the only sequence listing found by the Office does not anticipate the 127 mutation of SEQ ID NO 2 and thus will not anticipate the 172 mutation. Clearly by conducting the search for the 127 mutation of SEQ ID NO. 2, the Office inherently conducted the search on the 172 mutation of SEQ ID NO. 2. Accordingly, applicants request that all claims reciting the 172 mutation also be found allowable.

Discussion with Supervisor Jeffrey Siew

The undersigned attorney discussed this application with Jeffrey Siew and he has agreed, if needed, to participate in moving this application forward, especially in light of the latest of the Advisory Action. As such, applicants are requesting that if there is an outstanding issue that must be addressed, that Examiner Davis call the undersigned attorney so that a conference call can be arranged to move prosecution forward and if needed Supervisor Siew is willing to participate.

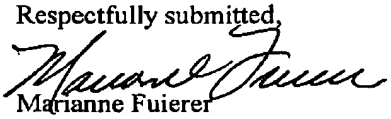
Fees Payable and Petition for Extension of Time.

Applicants hereby petition for a one (1) month extension of time, extending the deadline for responding to the August 3, 2004 Advisory Action to August 10, 2004. The entry of this petition results in a petition fee of $55.00. A credit card authorization form in the amount of $440.00 is included herein for payment of the petition fee ($55.00) and RCE fee ($385.00). The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Davis reconsider the patentability of claims 12, 23-25, 27-29 and 33-35 in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Davis is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,



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